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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/051,455	04/21/93	MASINOVSKY	B	FHIC16963

EXAMINER	
GAMBEL	

18M2/0511

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ART UNIT	PAPER NUMBER
1806	9

DATE MAILED: 05/11/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

2/14/94

☑ This application has been examined ☑ Responsive to communication filed on 1/27/94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 17-30 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☑ Claims 1-16 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 17-30 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

15. Claims 1-16 are canceled.
Claims 19-30 have been added.
Claims 17-30 are pending.

16. Applicant's arguments with respect to claims 17-18 and newly added claims 19-30 have been considered but are deemed to be moot in view of the new grounds of rejection.

It is noted that the instant application has been transferred to another examiner indicated at the end of the action.

17. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the form PTO-948 previously sent in Paper No. 4. Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes (see 7. Views).

18. The disclosure is objected to because of the following informality: "BALB/c" is the proper designation of this mouse strain.
Appropriate corrections are required.

19. 35 U.S.C. § 101 reads as follows:
"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

20. Claims 17-30 are rejected under 35 U.S.C. § 101 because the invention as disclosed is inoperative and therefore lacks utility. The specification fails to establish the utility of the claimed methods of modulating immune response by VCAM-specific agents as a therapeutic regimen in human patients. Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Harris et al. states that there is widespread acceptance that there is little future for the use of rodent monoclonal antibodies for in vivo human therapy (page 42, column 2) and that repeated dosing with chimeric antibodies is

ineffective due to residual anti-idiotypic responses (page 42, column 3)(Tibtech, 1993). Humanized antibodies present serious problems with immunogenicity, since the idiotype of such antibodies will contain unique amino acid sequences. In referring to the related adhesion molecule family, Harlan states that whether you go humanized antibody, peptide, soluble receptor or saccharide , its' is still a long way to a product that would be appropriate for the clinical setting (Edgington, Biotechnology, 1992; see entire document particularly, page 386, column 3, paragraph 4). Furthermore, Pelletier et al. (J. Immunol., 1992) teach that VCAM-1-specific antibody therapy was not effective in inhibiting allograft rejection in a mouse model (see entire document). Simmons et al. (Blood, 1992) teach that the instant VCAM-1-specific antibody 6G10 did not block the binding of hemopoietic progenitors in vitro (see entire document, particularly page 394, column 1). Therapeutic indices of immunosuppressive drugs can be species- and model-dependent. Applicant has disclosed limited inhibitory data by the VCAM-specific antibody 6G10 under defined in vitro conditions. Applicant has not provided any evidence a priori that establishes the efficacy of the claimed invention for the treatment of human disease. Therefore it does not appear that the asserted utility of the claimed method for treating humans would be believable prima facie to persons of skill in the art in view of the contemporary knowledge in the art. See MPEP 608.01 (p).

21. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

22. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure and failing to present the best mode contemplated by the applicant for carrying out the invention.

A) Applicant has not disclosed how to use VCAM-specific antibodies therapeutically in humans. There is insufficient written description of the invention with respect to the in vivo operability of VCAM-specific antibodies to use applicant's invention for the reasons discussed in detail in the previous rejection made under 35 U.S.C. § 101 (see paragraph 20). Although the VCAM-specific antibody 6G10 was able to inhibit lymphocyte binding under defined in vitro conditions, no examples have appeared in the application for predicting VCAM-specific immunotherapy for human diseases. Therefore it does not appear that the asserted operability of the claimed method and compositions for modulating immune responses in humans would be believable prima facie to persons of skill in the art in view of the contemporary knowledge in the art. It appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification alone.

B) It is unclear from the specification whether any VCAM-specific binding agent can modulate the immune response in vivo. Applicant has exemplified some in vitro inhibition of lymphocyte binding under defined conditions with the VCAM-specific antibody 6G10. As indicated above in section 20, Harlan states that whether you go humanized antibody, peptide, soluble receptor or saccharide , it's still a long way to a product that would be appropriate for the clinical setting as it applies to adhesion molecules (Edgington, Biotechnology, 1992; see entire document particularly, page 386, column 3, paragraph 4). Furthermore, Pelletier et al. (J. Immunol., 1992) teach that VCAM-1-specific antibody therapy was not effective in inhibiting allograft rejection in a mouse model (see entire document). Simmons et al. (Blood, 1992) teach that the instant VCAM-1-specific antibody 6G10 did not block the binding of hemopoietic progenitors in vitro (see entire document, particularly page 394, column 1). Therapeutic indices of immunosuppressive drugs can be species- and model-dependent. There is no evidence relating to the inhibition by any agent that binds VCAM to enable all of the agents embraced by the claims. The disclosure is not enabled for modulating the immune response with any VCAM-binding agent, all of which are embraced by the claims. Compositions comprising any agent that binds VCAM do not necessarily correlate with their ability to modulate immune response in vivo. Applicant has not set forth the metes and bounds of these VCAM-specific binding agents. The specification has not provided sufficient direction or guidance to one of skill in the art to properly select or administer any VCAM-binding agent that are required to practice the broadly claimed methods. It appears that undue experimentation would be required of one skilled in the art to practice the broadly claimed methods and their respective compositions using the teaching of the specification alone.

C) It is not clear from the specification whether 6G10-recognized molecules immunoprecipitated from TNF/IL-4 activated cultured human bone marrow stroma differ from VCAM (see specification, page 17, paragraph 1). These species include one with a molecular weight of 115-130 kD while the other was larger than 200 kD, as compared to the 100 kD of traditional VCAM-1. antigens recognized. Is the 115-130 kD species the seven domain (vs. six domain) VCAM structure? Is there any evidence of this? What is the greater than 200 kD structure? It appears that this antibody binds molecules other than the art-recognized VCAM. Therefore, the disclosure is not enabling for the antibody 6G10 to bind VCAM exclusively. Applicant has not set forth the metes and bounds of the target specificity of the 6G10 antibody, which was used to enable the instant invention. Therefore, it remains unclear whether the effects of 6G10 is mediated through VCAM alone or through multiple molecular species. The specification has not provided sufficient guidance to the specificity of the 6G10 antibody to enable the claimed invention's specificity for VCAM alone.

23. Claims 17-30 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification (see paragraphs 21-22).

24. Claims 17-30 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 17-30 are indefinite in the recitation of "modulating" the immune response or the interaction of VCAM-expressing cells because the characteristics of "modulating is not known. Modulation can occur either as stimulation or inhibition, for example. Applicant only has provided some evidence of an inhibitory function of a VCAM-specific antibody. No direction or guidance is provided to assist one skilled in the art in the selection of such agents that can modulate the immune response or associated cellular interactions in both a positive and negative fashion nor is there evidence provided that VCAM-specific agents can modulate such interactions therapeutically. It appears that undue experimentation would be required of one skilled in the art to practice the method of claim methods using the teaching of the specification alone.

Applicant should draft the method claims as inhibition or other appropriate terms that relate to the type of modulation enabled.

The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter.

25. Claims 20-29 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 20-29 are indefinite in the recitation of "mAb" because this term should be spelled out for clarity.

The amendments must be supported by the specification so as not to add any new matter.

26. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (f) he did not himself invent the subject matter sought to be patented.

27. Claims 22-30 are rejected under 35 U.S.C. § 102(f) because the applicants did not invent the claimed subject matter. The claimed modulation of VCAM-expressing cells by the 6G10 antibody as described in the instant application are cited in Simmons et al. (Blood, 1992). This reference presents an ambiguity with regard to inventorship because the named authors includes Longenecker, Berenson, Torok-Storb, who are not listed as inventors herein. This reference is written as "we show". This reference says nothing about inventorship. Because of this ambiguity, it is incumbent on applicants to provide a satisfactory showing which would lead to a reasonable conclusion that applicants alone are the inventors of the claimed invention. See In re Katz, 687 F.2d 450, 215 USPQ 14(CCPA 1982). To resolve the ambiguity, applicants may file declarations by the non-applicant co-authors of the references disclaiming the invention or a declaration by applicant setting forth the facts which provide an explanation as to why the non-applicant co-authors are not inventors. See MPEP 715.05.

28. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

29. Claims 17-30 are rejected under 35 U.S.C. § 103 as being unpatentable over Osborn et al. (1449, #029; Cell, 1989), Elices et al. (1449, #030; Cell, 1990), or Newman et al. (1449, #A1; U.S. Patent No. 5,011,778) in view of Graber et al. (J. Immunol., 1990), Rice et al. (1449, #028; Science, 1989), Rice et al. (J. Exp. Med., 1990), Lewinsohn et al. (Blood, 1990), Shimizu et al. (Immunol. Rev., 1990) or Prober et al. (1449, #014; Am. J. Pathol., 1988). Claims 17-30 are drawn to the modulation of VLA-VCAM cell interactions by VCAM-specific binding agents. Osborn et al. teach the expression of VCAM and its role as a cell adhesion molecule in normal tissue development and inflammatory conditions (see entire document). Osborn et al. also teach that VCAM-specific antibodies can block VLA-mediated binding and relate to this inflammatory responses (see page 1208, column 2). Osborn et al. also teaches that VCAM-dependent pathways would provide intervention points for correction of pathologies associated with acute and chronic inflammation. Elices et al. extend these observations to indicate that VLA-4 on leukocytes interacts with VCAM on endothelial cells and this can be block by antibodies (see entire document). Similarly, Elices et al. relate this interaction to normal and disease states involving leukocytes and their adhesion and recruitment. Newman et al. teach the use of 1E7/2G7-specific antibodies to inhibit leukocyte inflammatory responses (see entire document). As Graber et al. teaches, the 1E7/2G7 antigen is VCAM (see page 829, Note Added in Proof). Graber et al. is provided to indicate the 1E7/2G7 was VCAM and not to serve as prior art per se. These references differ from the claimed invention by not describing the 6G10 antibody or IL-4

activation per se. However, the specificity of the claimed intervention is VCAM and it would not have critical to the targeting the VCAM adhesion molecule that was activated through IL-4 or through other stimulants. Rice et al. (Science, 1989)teach the expression of INCAM-110 (VCAM) on endothelial cells and dendritic cells (see page 1305, column 1). Rice et al. (J. Exp. Med., 1990) extends this observation to localize INCAM-110 (VCAM) expression at inflammatory sites and on dendritic cells as well as its role in lymphocyte adhesion and activation (see entire document, particularly, page 1372, paragraph 3). Lewinsohn et al. teach the expression of adhesion molecules on human hemopoietic progenitor $CD34^+$ cells and draws attention to MEL-14, the murine analog of VLA (see entire document, particularly page 594). Shimuzu et al. review the art-known role of VLA-4 in T cell adhesion and stimulation and the identification of its ligand VCAM (see entire document, particularly pages 132-137 and Note Added in Proof). Prober et al. teach the art-known role of adhesion molecules in leukocyte adhesion and activation and the targeting of such interactions in manipulating pathologic diseases (see entire document).

Therefore, the art recognized the role of interfering adhesion interactions to modulate immune responses, including through VLA/VCAM pathways. VCAM was known to be present on endothelial cells and dendritic cells, both intimately involved in T cell adhesion and activation. VCAM's ligand VLA was known to be associated with either T cells or bone marrow precursors. The art teaches the generations of VCAM-specific reagents as taught by Osborn, et al., Elices et al. and Newman et al.; therefore the skilled artisan would have derived the claimed 6G10 antibody of the instant claims by routine experimentation. The skilled artisan would have use such VCAM-specific reagents to inhibit lymphocyte or hemopoietic interactions with VCAM-expressing cells to condition patients for various inflammatory conditions or hemopoietic reconstitution. One of ordinary skill in the art at the time the invention was made would have been motivated to select and evaluate the efficacy of VCAM-specific agents in a therapeutic regimen to modulate various inflammatory responses either in peripheral or central hemopoietic organs. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

30. No claim is allowed.

31. It is noted that applicant did not supply the references associated the Information Disclosure Statement, filed 2/14/94 (Paper No. 8). The examiner has considered references A1-A2 and D1-D5 but has not considered references B1-B12, C1-C4 and E1-E7 at this time.

32. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4227.

33. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1806.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

Phillip Gambel, Ph.D.
May 9, 1994

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PRIM[illegible]AMINER
GROUP 1800